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In-vivo proton MR-spectroscopy of the human brain: Assessment of N-acetylaspartate (NAA) reduction as a marker for neurodegeneration

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Summary. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive method to investigate changes in brain metabolite composition in different cerebral diseases.

We performed proton spectroscopy in patients with dementia of the Alzheimer's type (AD) and in patients with motor neuron disease (MND) with the aim to detect the specific metabolic pattern for these neurodegenerative disorders.

In the MND group we found a significant reduction of NAA/tCr metabolite ratios in the motor cortex, which correlates with the disease severity and the clinical lateralization of neurological symptoms and further decreases in the time course of the disease. In AD patients a reduction of NAA/tCr was observed in the medial temporal lobe.

Since NAA is exclusively expressed in neurons as shown by immunohistochemical studies, reduced NAA levels suggest neuronal loss or dysfunction in the observed regions.

The observed regional metabolic alterations reflect the neuronal basis of the characteristic neurological symptoms in AD (dementia) and MND (muscular palsy) and mirrors the disease progress over time.

Key words: Proton MR spectroscopy – Neurodegeneration – N-Acetylaspartate – Alzheimer's disease – Motor neuron disease

Introduction

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive method to investigate changes of the tissue metabolite composition in different brain diseases. At long echo times (TE $>$ 100 ms) the resonance lines of the N-acetyl groups, mainly N-acetylaspartate (NAA), of choline containing compounds (Cho), and of total creatine (tCr) including creatine and phosphocreatine, can be detected in 1H-MR spectra in-vivo (Jenkins et al., 1998).

In this study we performed proton spectroscopy in patients with dementia of the Alzheimer's type (AD) and in patients with motor neuron disease (MND) with the aim to detect a specific metabolic pattern for each of these two neurodegenerative disorders. Alzheimer's disease, the main cause of dementia in elderly subjects, is characterized by early neuronal loss of medial temporal lobe structures, including the hippocampus. MND, respectively ALS (amyotrophic lateral sclerosis), is characterized by a progressive loss of neurons located in the motor cortex and the brain stem. Consequently, MRS was performed in the MTL of AD patients and in the motor cortex of MND patients. The selected regions represent the areas of earliest and most severe neuronal damage in either disease, and their degeneration accounts for the clinical symptoms of dementia in AD and muscular palsy in MND.

Material and methods

Study subjects

34 patients (mean age 70 ± 8 years, 10 male, 24 female) who met the NINCDS/ADRDA (McKhann et al., 1984) criteria for probable AD, and 22 healthy subjects (mean age 69 ± 9 years, 12 male, 10 female) were included in the study. 16 AD patients (mean age 70 ± 9 years, 6 male, 10 female), who participated in the first cross-sectional study, were included in the follow-up.

70 patients with ALS according to the El Escorial criteria (Brooks, 1994) were recruited (mean age 55 ± 13 years, 39 male, 31 female). No patient had a history of any other neurological disease. In 17 patients follow-up investigations were performed within 28 months. 48 healthy volunteers (mean age 52 ± 18 years, 31 male, 17 female) without history of any neurological disease served as controls.

The study protocols were approved by the ethical committee of the University of Bonn and are in accordance with the declaration of Helsinki. All patients and control subjects gave informed consent before participation.

Magnetic resonance examinations

Magnetic resonance (MR) investigations were performed on 1.5 Tesla whole body MR systems Gyroscan S15/ACS II and Gyroscan ACS-NT (Philips Medical Systems, Best, The Netherlands) using a head coil suited for magnetic resonance imaging (MRI) and proton MR spectroscopy (^{1}H-MRS). For image guided localization of the spectroscopic volumes of interest (VOI), diagnostic MRI in transversal, coronal and sagittal slice orientation was performed in patients and controls.

In the MND group two cubic VOI of 30 ml were placed anterior to the central sulcus in the motor cortex and subjacent white matter in both hemispheres. The VOIs were angulated in the way that the upper boundaries of the cubes were aligned parallel with the brain surface in the sagittal and the coronal plane. The primary motor areas of the hand and upper limb within Brodmann area 4 and 6 were included (Fig. 1a,b).

To determine the lateralization of ^{1}H-MRS findings the quotient of metabolite ratios obtained in the right and in the left hemisphere was calculated. To further establish an index for asymmetry of spectroscopic findings this quotient was transformed to express the percental difference between measurements in the right and in the left motor cortex using the following equation:

$$pMLR = \left(1 - \frac{metabolite\ ratio_{\ right}}{metabolite\ ratio_{\ left}}\right) \cdot 100\%$$

This index quotient will be addressed to as the percental metabolic lateralization ratio (pMLR). In cases with bulbar symptoms an additional VOI of about 8 ml was placed in the brainstem covering the pons and upper medulla (Fig. 1c).

In the AD patients first a cubic VOI of about 25 ml was positioned in parallel angulation to the left MTL including the hippocampus (Fig. 2). A second VOI of 30 ml was placed in the left motor cortex in the same way as in the MND patients (Fig. 1a,b).

^{1}H-MRS spectra were acquired with PRESS volume selection (Bottomley, 1987) and water suppression performed by two frequency modulated 180° inversion prepulses (Shen and Saunders, 1993). With TR/TE 2000/272 ms and 128 signal averages the acquisition for each spectrum took about 4 minutes. Analysis of the spectra was performed with the manufacturer supplied spectroscopy software package of the MR system. Relative metabolite concentrations for N-acetylaspartate (NAA), choline (Cho) and total creatine tCr including phosphocreatine and creatine were determined by Lorentz-curve fitting of the corresponding resonances in the frequency spectra. Typical proton spectra are displayed in Figs. 3 and 6.

In some patients of both groups absolute concentrations of NAA, tCr and Cho in the VOIs described above were determined using the brain water signal as an internal reference (Kreis et al., 1993). For this purpose additional proton magnetic resonance spectra were acquired without water suppression, with TR/TE 3000/272 ms and averaged over 16 or 32 FIDs yielding NAA/H_2O signal ratios. In the postprocessing of these unsuppressed spectra, polynomial baseline subtraction removed the broad Lorentzian slopes of the water resonance curve underlying the much smaller metabolite peaks. To determine NAA/H_2O concentration ratios by extrapolation to TR ∞ and TE 0, T2 relaxation times and relative fractions of CSF and tissue water within the VOI were obtained by a bi-exponential fit to a series of unsuppressed spin echo spectra with TE 30/70/136/272/400/700/1,000 ms, and 4 signal averages each. Errors due to variations in the assumed T1 values of mixed gray/white matter (800 ms) and CSF (3,000 ms) were minimized using a long TR of 6,000 ms. Metabolite T1 and T2 values were not measured on an individual basis, but taken from our comparative analysis in healthy volunteers and ALS patients published previously (Block et al., 1998). Metabolite concentrations were expressed as mmol/l brain tissue using a mixed gray/white matter water content of 72% corresponding to 40 mol/l.

Metabolic ratios and absolute metabolite concentrations determined from different brain areas in AD and MND patients were compared to spectroscopic data acquired from the same brain regions with identical measurement protocols in age-matched healthy volunteers.

Statistical analysis

Group comparisons of metabolic ratios were performed using the student t-test to assess differences between patients and controls.

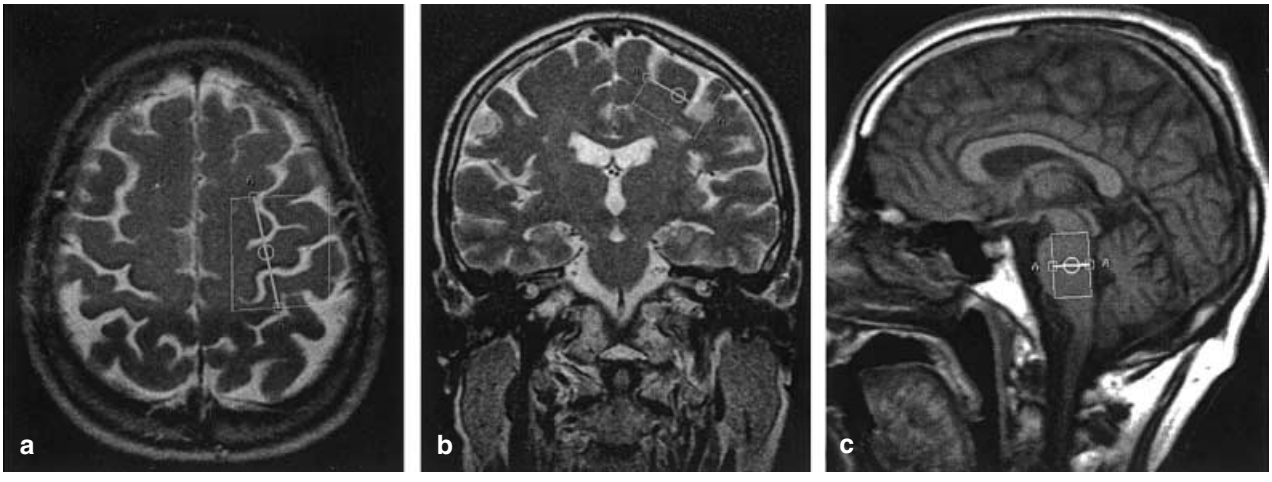

Fig. 1. Transversal (**a**) and coronal (**b**) magnetic resonance images demonstrating the localization of a motor cortex volume of interest (VOI). ^{1}H-MRS spectra were aquired from a cubic VOI of 40 × 30 × 25 mm placed anterior to the central sulcus in the motor cortex and subjacent white matter. Sagittal MRI (**c**) displays the localisation of the a 20 × 25 × 15 mm VOI in the pons/upper medulla

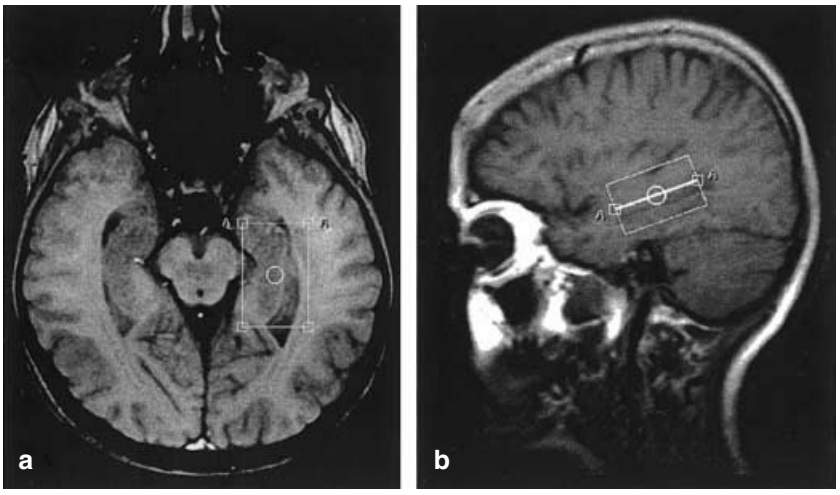

Fig. 2. MR image-guided localization of spectroscopic volumes of interest (VOI) in the left medial temporal lobe displayed on transversal (**a**) and sagittal MRI (**b**)

Table 1. Mean metabolite ratios and absolute concentrations of proton metabolites acquired from the motor cortex and the pons of patients with MND/ALS compared to healthy controls

	n	NAA/Cho	NAA/tCr	Cho/tCr	n	NAA	Cho	tCr
motor cortex						(mmol/L)	(mmol/L)	(mmol/L)
ALS	120	*2.07 (0.27)	*2.64 (0.30)	*1.29 (0.15)	60	*12.3 (1.3)	2.1 (0.4)	*6.8 (0 .8)
Controls	60	2.45 (0.21)	2.92 (0.28)	1.20 (0.12)	20	13.9 (0.9)	2.1 (0.2)	7.4 (0.8)
p		<0.0001	<0.001	<0.005		<0.001	n.s.	<0.05
pons								
ALS	25	*1.51 (0.24)	3.70 (1.12)	2.50 (0.72)		–	–	–
Controls	10	1.84 (0.24)	4.13 (1.02)	2.27 (0.55)		–	–	–
p		<0.005	n.s.	n.s.				

NAA, N-acetylaspartate; *Cho*, choline containing compounds; *tCr*, total creatine; *ALS*, amyotrophic lateral sclerosis; *n.s.*, not significant; indicated p-values refer to student-t test

Correlation of the pMLR score and the laterality of clinical symptoms was assessed with the Pearson correlation coefficient. Calculations were performed with the SPSS 9.0 software package (SPSS Inc., Chicago, Illinois, USA).

Results

MND patients

Group comparison of ALS patients and controls revealed a significant reduction of the NAA/Cho ($p < 0.0001$) and the NAA/tCr ratio ($p < 0.001$) in the motor cortex of ALS patients, whereas the Cho/(P)Cr ratio ($p < 0.005$) was significantly elevated. ALS patients with clinical evidence of bulbar pathology showed a significant decrease in NAA/Cho ($p < 0.005$) in the pons spectra with a non-significant trend of lower NAA/tCr and no differences for Cho/tCr in comparison with control spectra. Further analysis of spectroscopic data from absolute quantification showed a significant reduction in the concentrations of NAA ($p < 0.001$) and tCr ($p < 0.05$) in the motor cortex of ALS patients, while the concentration of Cho compounds remained unchanged. Means and standard deviations of these data are summarized in Table 1.

Intra-individual comparison of metabolic ratios from the left and right brain hemisphere yielded different metabolic pathology, which was either left or right lateralized in individual subjects (Fig. 3). This individual laterality is expressed with the pMLR score. There was a significant correlation ($p < 0.01$) of this score and the lateralization of clinical symptoms. This relationship is illustrated in a error bar graph of pMLR (values indicating a NAA/Cho ratio to the disadvantage of one motor cortex) and most often corresponds to a contra-lateral predominance of clinical symptoms (Fig. 4).

Follow-up examinations in ALS patients varied between subjects. Figure 5 illustrates the temporal development of NAA/Cho ratios in individual patients.

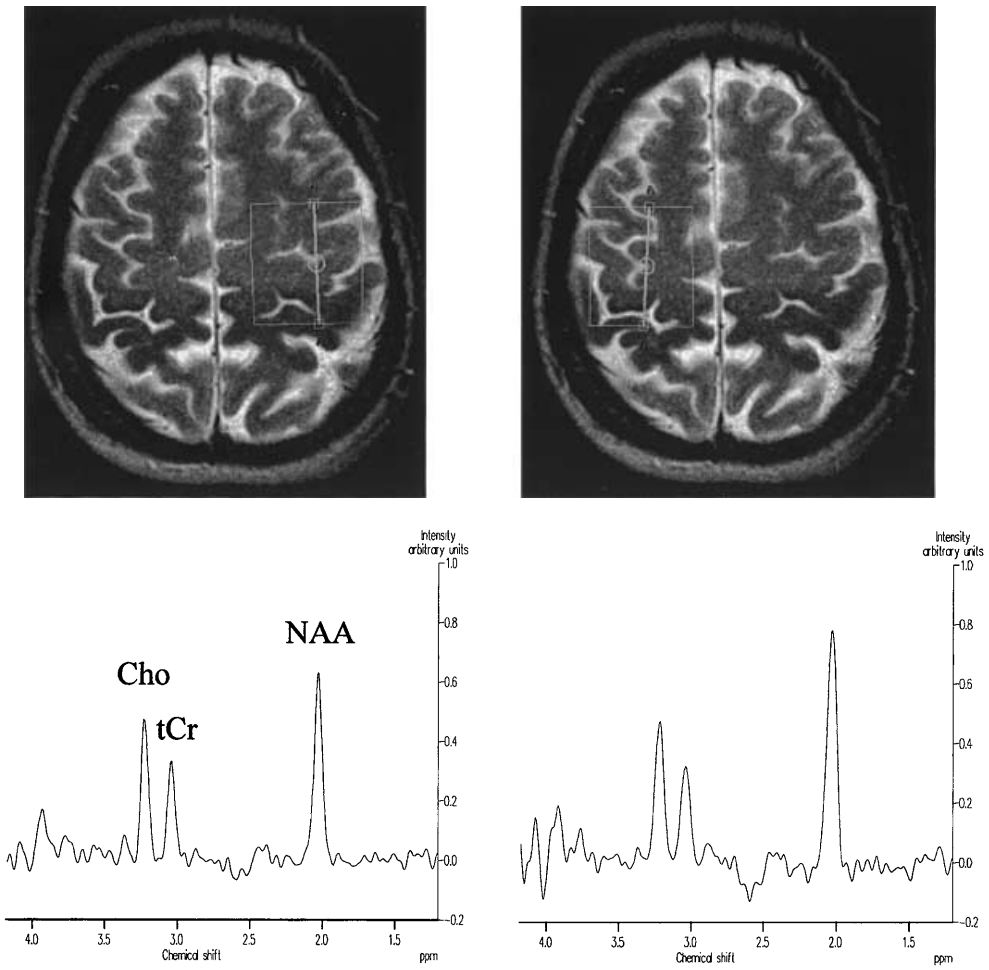

Fig. 3. Example of lateralized ^{1}H-MRS spectra in a patient with ALS. Decrease of NAA is more pronounced in the spectrum acquired from the left hemisphere displayed on the left side

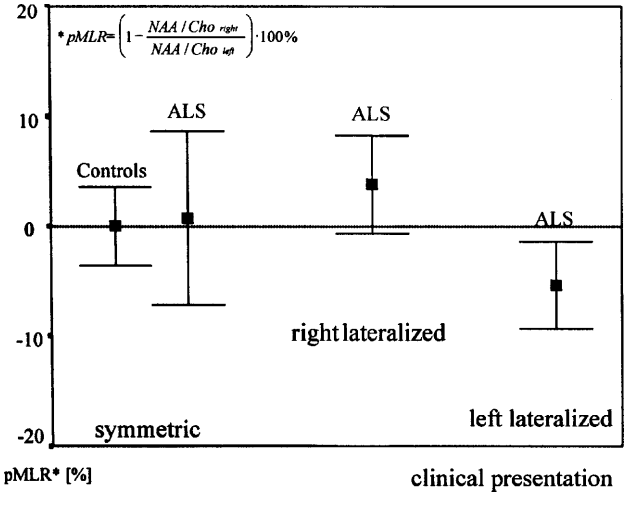

Fig. 4. Error-bar graph displayed the correlation between clinical presentation and lateralization of metabolic pathology in patients with ALS

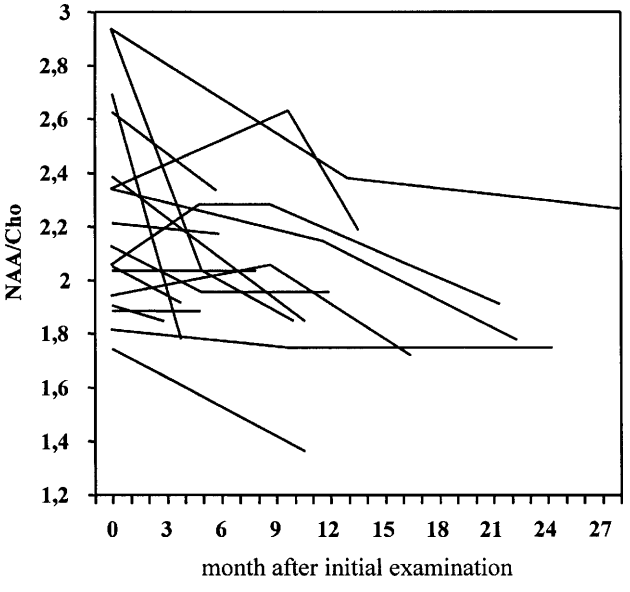

Fig. 5. Longitudinal time course of NAA/Cho in individual patients with ALS

Table 2. Mean metabolite ratios and absolute concentrations of proton metabolites acquired from the medial temporal lobe and the motor cortex of patients with Alzheimer' disease (AD) compared to healthy controls

	n	NAA/Cho	NAA/tCr	Cho/tCr	n	NAA	Cho	tCr
MTL						[mmol/L]	[mmol/L]	[mmol/L]
AD initial+	34	*1.42 (0.19)	*2.26 (0.40)	1.60 (0.22)	16	10.7 (1.9)	2.7 (0.7)	7.7 (2.1)
AD follow-up	16	1.37 (0.24)	2.04 (0.43)	1.49 (0.21)				
Controls−	22	1.57 (0.27)	2.74 (0.79)	1.71 (0.33)	9	11.5 (1.8)	2.7 (0.4)	6.9 (1.9)
p (+ vs −)		<0.05	<0.005	n.s.	n.s.	n.s.	n.s.	
motor cortex								
AD initial+	26	2.18 (0.38)	2.70 (0.48)	1.22 (0.25)	10	12.9 (1.0)	1.9 (0.2)	6.8 (0.8)
AD follow-up	12	2.17 (0.21)	2.74 (0.37)	1.27 (0.21)				
Controls−	22	2.37 (0.29)	2.82 (0.30)	1.21 (0.16)	11	13.7 (1.0)	2.1 (0.3)	7.6 (0.8)
p (+ vs −)		n.s.	n.s.	n.s.		n.s.	n.s.	n.s.

NAA, N-acetylaspartate; *Cho*, choline containing compounds; *tCr*, total creatine; *AD*, Alzheimer's disease; *n.s.*, not significant; indicated p-values refer to student t-test

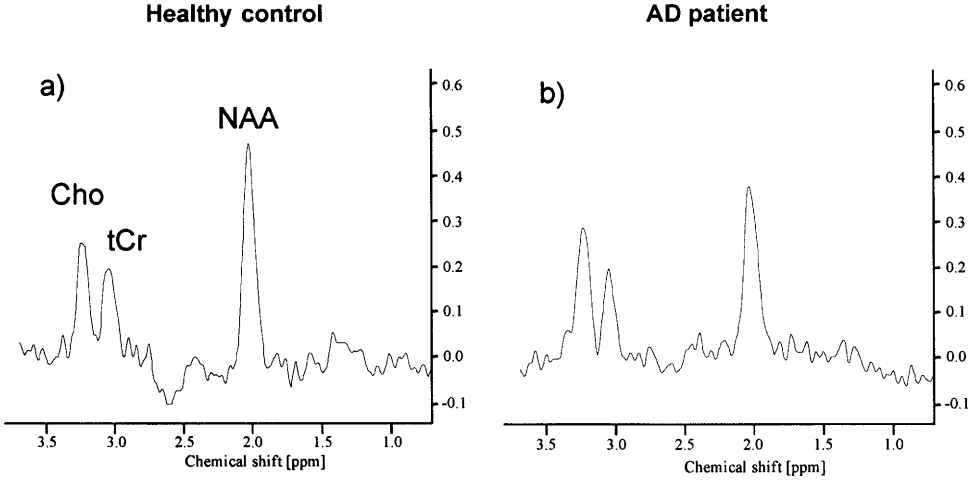

Fig. 6. Proton spectra from a 77-year old female AD patient in comparison to those of a 71-year old female healthy volunteer

Although the plot shows a general trend for a further reduction in NAA/Cho over time, the velocity of the degenerative process appears to vary substantially.

AD patients

Single volume spectroscopy of the MTL in patients with Alzheimer's disease revealed a significant reduction in NAA/Cho ($p < 0.05$) and in NAA/tCr ($p < 0.005$). For Cho/tCr no significant changes were observed. Comparison of spectroscopic data determined from motor cortex spectra yielded no significant differences between AD patients and controls in any metabolic ratio.

Results in absolute quantification of metabolites in these two regions showed no significant changes. In the MTL and in the motor cortex there was a trend towards decreasing concentrations for NAA. Concentrations in choline compounds were equal to controls in both regions. The tCr concentration was increased in the MTL and was decreased in the motor cortex in comparison to controls. Mean values and standard deviations of spectroscopic data are given in Table 2.

Follow-up investigations in AD patients confirmed these findings by reproducing changes in the MTL. A trend to progressive reduction in metabolite ratios NAA/tCr and NAA/Cho was observed, which however did not reach significance. Means and standard deviations of metabolite ratios acquired from patients in comparison to the control group are summarized in Table 2.

Discussion

The main findings of this study are significant metabolic changes in the MTL of patients with Alzheimer's

disease and significant differences of the metabolic distribution in the motor cortex of patients with MND in comparison with healthy controls. In the MTL of AD patients a significant reduction in NAA/Cho and NAA/tCr was found. Although absolute quantification of metabolites yielded no significant changes, the observed trends for decreased NAA and increased tCr concentrations are consistent with the changes in metabolite ratios. Especially, the diametrical development of NAA and tCr could explain, the greater changes of NAA/tCr than of NAA/Cho ratios.

Similar changes were found in the motor cortex of MND patients with a significant reduction in NAA/Cho and NAA/tCr, but additionally with a significant increase in Cho/tCr. As well as in the MTL of the AD patients, in the motor cortex of MND patients the absolute concentrations of NAA were reduced, while Cho concentration remains unchanged compared to concentrations in healthy controls. In contrast to increased tCr concentration in the MTL of AD patients, in the motor cortex of MND patients we found a significant decrease in tCr. The observed smaller differences in motor cortex NAA/tCr in MND patients compared to the NAA/Cho ratio thus results from the unidirectional development of NAA and tCr concentrations.

NAA is exclusively expressed in neurons as shown by immunohistochemical studies (Simmons et al., 1991; Urenjak et al., 1992), and represents a marker for neuronal integrity. A reduction of NAA has been reported in various brain regions in AD (Passe et al., 1995) and other neurodegenerative disorders (Block et al., 1998; Duyn et al., 1995; Karitzky et al., 1999; Tedeschi et al., 1997). Cho represents a constituent of cell membranes and has been found to be elevated in AD in some (Block et al., 1995; Lazeyras et al., 1998; MacKay et al., 1996; Meyerhoff et al., 1994; Pfefferbaum et al., 1999), but not all studies (Christiansen et al., 1993; Ernst et al., 1997; Heun et al., 1997; Miller et al., 1993; Moats et al., 1994; Parnetti et al., 1997; Rose et al., 1999; Schuff et al., 1998). Results from absolute quantification in this study support the latter studies.

Total creatine, which is engaged in the cells energy metabolism, has been reported to remain stable in AD (Pfefferbaum et al., 1999; Schuff et al., 1997) and other neurodegenerative disorders (Chan et al., 1999; Pioro et al., 1994). Changes of NAA and Cho are therefore commonly assessed in relation to tCr. One recent follow-up study of AD patients provided evidence for decrease of tCr over time in cortical regions (Adalsteinsson et al., 2000). These findings are in agreement with the data from our longitudinal study of the motor cortex in MND patients. Future studies will need to assess the validity of metabolic ratios in the longitudinal monitoring of neurodegeneration.

An inherent limitation of ^{1}H-MRS is the lack of specificity of the observed changes for any disease. In addition to neurodegenerative disorders, a reduction of NAA has been reported in vascular (Capizzano et al., 2000; Wardlaw et al., 1998), metabolic (Rajanayagam et al., 1997) and inflammatory (De Stefano et al., 2001) diseases. To circumvent this limitation, recent studies have investigated those brain regions that specifically characterize the distribution of neuronal damage in an individual disease (Pioro, 1997) (Jessen et al., 2000) (Block et al., 1998).

The observed regional metabolic alterations correlate well with the characteristic neurological symptoms in AD and MND and seem to follow the disease process over time.

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